No. 12-398

IN THE
Supreme Court of the United States

THE ASSOCIATION FOR MOLECULAR PATHOLOGY, ET AL.,
Petitioners,

v.

MYRIAD GENETICS, INC., ET AL.,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Federal Circuit

BRIEF OF GENFORMATIC LLC AS *AMICUS CURIAE* IN SUPPORT OF PETITIONERS

DANIEL BINFORD WEAVER
6301 Highland Hills Drive
Austin, Texas 78731
(512) 565-4693

EARL LANDERS VICKERY
Counsel of Record
LAW OFFICE OF LANNY VICKERY
3007 Dancy Street
Austin, Texas 78722
(512) 435-6666
(lanny@justiceseekers.com)

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INTEREST OF THE *AMICUS CURIAE*[1]

Genformatic LLC is a company based in Austin, Texas, engaged in the business of genome sequencing and analysis. All genome sequencing currently practiced involves isolating, purifying, and fragmenting DNA into varying lengths of nucleotide sequences. Thus, whether and to what extent third parties hold intellectual property rights to portions of those nucleotide sequences affects or impairs the ability of scientists, clinicians, and innovators to practice genome analysis and improve the technology of DNA sequencing. Patents on DNA sequences that occur naturally in the genomes of organisms, including humans, also affect or impair the ability of companies such as Genformatic to engage in the business of DNA sequencing and analysis for medical, agricultural, pharmacological, and consumer genomics purposes. Genformatic is concerned that allowing patents to issue on nucleotide sequences that occur naturally in human DNA not only violates this Court's traditional prohibition against patenting natural phenomena but also hinders the advancement of science and technology in this vital area.

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[1] Pursuant to Supreme Court Rule 37.6, counsel for *amicus* Genformatic represents that none of the parties or their counsel authored this brief in whole or in part and that no person or entity other than *amicus* or its counsel made a monetary contribution to its preparation or submission. Petitioners have lodged a blanket consent to the filing of *amicus* briefs, and written consent by respondents to the filing of this brief has been lodged with the Clerk of the Court.

SUMMARY OF ARGUMENT

Sequencing of the human genome represents a revolutionary advancement in the life sciences and presents an opportunity to advance our knowledge of ourselves beyond the conception of even our most visionary thinkers a few decades ago. Since the implementation of the first genome sequencing in the mid-1970s, and especially in the past few years, the speed of sequencing operations has exploded as the cost has plummeted. As with other revolutionary technologies such as personal computers and cell phones, we are approaching an inflection point at which genome sequencing and analysis will become a realistic possibility for the general population. This will allow health care providers to counsel and treat patients based not on generalized norms, but on individual genetic profiles. With this knowledge, the practice of medicine and the development of therapeutic regimens will gradually depend less on trial and error and more on targeted analysis and treatment. Respondent Myriad has recognized the importance of whole genome sequencing ("WGS") and has expressly represented that the claims in its patents "do not preempt or preclude" it. Opp. 17. Whether Myriad or any other holder of such patent rights would make this concession outside this litigation is less certain.

Myriad does not dispute that its claims cover the exact sequences of nucleotide base pairs that occur naturally in human DNA. *See*, *e.g.*, U.S. Patent No. 5,747,282 (filed May 5, 1998) (" '282 patent"), JA822 (claims 1-7); U.S. Patent No. 5,837,492 (filed Nov. 17, 1998) (" '492 patent"), JA1028 (claims 1-10). But it contends that, because it has claimed "isolated" nucleotide sequences, it has invented something and should be allowed a patent on that section of the

human genome sequence. To put Myriad's contention into context, consider that the human genome contains approximately 3 billion nucleotide base pairs. Myriad claims patent rights in sequences as short as 15 base pairs. JA822 (claims 5-6), 1028 (claim 5). With respect to one such claim, researchers observed that Myriad's claimed sequences occurred approximately 340,000 times on chromosome 1 alone, and when extrapolated to the entire human sequence confirms their probable occurrence more than four million times in any human genome.[2]

As an initial step, all genome sequencing techniques currently practiced require randomly fragmenting a DNA molecule into lengths of generally between 30 and about 1,000 base pairs. Sequencing of these individual fragments generates corresponding sequences of nucleotides, called "reads." It is inevitable that DNA molecules having one or more of the nucleotide sequences claimed in Myriad's patents will appear in many different sequence reads produced during sequencing of any human genome.

Nonetheless, Myriad relies heavily on Professor Holman's articles to "debunk the myth" that WGS infringes its patents. *See* Opp. 6, 16. Analysis of his actual methodology and findings reveals that, far from "debunking the myth," Professor Holman underscores the danger of allowing patents on naturally occurring nucleotide sequences. In his study, he identified 4,270 U.S. patents that previously had

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[2] *See* Thomas B. Kepler et al., *Metastasizing Patent Claims on BRCA1*, 95 GENOMICS 312, 313 (May 2010) ("Kepler"), *available at* http://www.sciencedirect.com/science/journal/08887543/95/5.

been labeled as "gene patents."[3] Although he has both a Ph.D. in molecular biology and a law degree, however, he examined only 12.5% of those patents "to make my task manageable." Holman, NATURE BIOTECHNOLOGY at 241. Reading all the claims in this limited sample, he found that almost 70% of the patents he reviewed claimed "DNA molecules that correspond in sequence to at least some portion of a human gene." *Id.* Mathematically extrapolating his findings to all 4,270 patents, his research indicates that there are 2,956 U.S. patents that claim a portion of the human genome – the code of life that occurs naturally in the genetic makeup of every human being. Despite such an overwhelming number of patents, however, Professor Holman advocates reliance on the "notoriously unpredictable undertaking" of claim construction to conclude that a court would ultimately find that gene sequencing did not infringe patents claiming overly broad sequences of DNA. *Id.*

Professor Holman's position is consistent with other advocates of the patentability of naturally occurring nucleotide sequences. They insist that it is a better policy to allow such patents under 35 U.S.C. § 101 and to police overreaching through claim construction, anticipation under § 102, obviousness under § 103, and the written-description requirement of § 112. But this Court soundly rejected such an approach in *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289, 1303 (2012).

Furthermore, in its 2010 report to the Department of Health and Human Services, the Secretary's

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[3] Christopher M. Holman, *Debunking the Myth that Whole-Genome Sequencing Infringes Thousands of Gene Patents*, 30 NATURE BIOTECHNOLOGY 240, 241 (Mar. 2012) ("Holman").

Advisory Committee on Genetics, Health, and Society observed that the patenting of human genes gives rise to great unpredictability and uncertainty, threatening a "patent thicket" that can inhibit future innovation.[4] This is exactly the danger the court recognized in *Mayo*. *See* 132 S. Ct. at 1303. The Court should not allow those engaged in genome sequencing to be deprived of such a "basic tool[]" of their "scientific and technological work." *Id*. at 1293 (internal quotation marks omitted).

ARGUMENT

I. GENOME SEQUENCING INVOLVES ISOLATING, PURIFYING, AND FRAGMENTING DNA MOLECULES INTO SEQUENCE LENGTHS THAT INEVITABLY FALL WITHIN THE EXPRESS LANGUAGE OF MYRIAD'S CLAIMS

Genformatic believes that a description of gene sequencing will aid the Court in understanding the issues in this appeal. A brief review will put that description in context.

A. An Overview of the Genome

DNA provides the blueprint by which organisms, including humans, are made. The human genetic code is carried in molecules of DNA, arranged in 23 pairs of chromosomes, contained in every cell of the body. Each DNA molecule exists in the form of two

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[4] U.S. Dep't of Health & Human Services, *Report of the Secretary's Advisory Committee on Genetics, Health, and Society: Gene Patents and Licensing Practices and Their Impact on Patient Access to Genetic Tests* 51 (Apr. 2010) ("HHS Report"), *available at* http://oba.od.nih.gov/oba/SACGHS/reports/SACGHS_patents_report_2010.pdf.

separate strands, bound together in a double helix. Each strand contains a sequence of nucleotides: adenine, guanine, cytosine, and thymine, "A, G, C, and T" respectively. These are the only nucleotides in DNA, so the alphabet of heredity consists of only four letters. Contiguous nucleotides on each strand are linked together in linear order by a series of phosphodiester bonds.

Hydrogen bonds bind nucleotides on opposing strands together. The bonds form selectively: A on one strand always pairs with T on the other, while G always pairs with C on the opposite strand. The order in which these nucleotides appear defines an individual's genome.

An essential part of the central dogma of molecular biology is the concept of a "gene." As originally conceived more than 50 years ago, a gene is a DNA sequence transcribed by cellular machinery into messenger RNA, which in turn is translated into a protein or an amino acid polypeptide. Scientists initially assumed that proteins performed all the work required for life, conducting essential enzymatic or biochemical reactions, mediating cellular interactions, precipitating immune responses, and facilitating other functions useful for propagation or survival.

Frequently, there are differences in the expected DNA sequence between two organisms of even the same species. These differences appear in such forms as single nucleotide polymorphisms, or sequence deletions, insertions, or duplications. These changes are often described as "mutations" or "sequence variants." Some but not all of these DNA mutations or sequence variants may manifest in protein changes or alterations in the amino acid sequence of a polypeptide.

Other DNA mutations may alter regulatory features of genes and result in differences in gene expression, in post-transcriptional modifications to RNA, or in post-translational changes to proteins. Yet other genomic variation may impact interactions among genes or result in modifications to the three-dimensional structure of DNA, as well as a growing catalogue of other consequences.

Stated differently, scientists now appreciate that mutations may alter more than the amino acid sequence of a protein. Other effects include modifications to gene transcription (DNA => RNA), RNA splicing, and translation (RNA => protein), and an increasing panoply of genomic interactions. The detection of variants in an individual's DNA sequence allows one to use any previously documented association of those variants with disease susceptibility or drug safety or efficacy to assess an individual's genomic heath risk. That is, one may forecast an individual's probability of exhibiting particular traits or health conditions based upon the detected sequence variation in that person's genome. Disease predisposition and drug-risk assessment are among the primary reasons to do genetic testing in humans and other organisms.

B. A Gene Is Any Sequence of Nucleotides That May Contribute to the Functional and Heritable Characteristics of an Organism

The conception of a gene has evolved considerably in the past 50 years. First articulated as the heritable unit that produces a metabolic enzyme to do the biochemical work of the cell, the concept of a "gene" has now evolved to include any nucleic acid sequence

or any combination of nucleotide sequences that produces functional consequences for an organism.[5]

Gregor Mendel, the father of genetics, conceived of a discrete unit conveying inherited characteristics or traits from parent to offspring. Although he was not the first to use the term "gene," Mendel was the first conceptually to distinguish the genotype (the allelic combination of heritable units) from phenotype (the traits or characteristics exhibited by an organism).[6]

Years later, in 1941, Beadle and Tatum developed the hypothesis of one gene–one enzyme, and proposed the mechanism of gene mutation after their experiments exposing mold to X-rays led to errors in metabolic activity.[7] For several years, some erroneously interpreted their work to support the view that proteins themselves were the heritable, information-containing biological molecules.

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[5] *See* Mark B. Gerstein et al., *What is a gene, post-ENCODE? History and updated definition*, 17 GENOME RES. 669 (June 2007). *available at* http://genome.cshlp.org/content/17/6/669.full.pdf+html.

[6] *See* Gregor Mendel, *Versuche über Pflanzenhybriden*, *in* 4 *Verhandlungen des naturforschenden Vereines in Brünn* 3 (1865). For the English translation, see Gregor Mendel, *Experiments in Plant Hybridization* (C.T. Druery & William Bateson trans., 1901) (1865), *available in updated form at* http://www.esp.org/foundations/genetics/classical/gm-65.pdf.

[7] *See* George W. Beadle & Edward L. Tatum, *Genetic Control of Biochemical Reactions in Neurospora*, 27 PROC. NAT'L ACAD. SCI. 499 (Nov. 1941), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1078370/pdf/pnas01634-0009.pdf.

Shortly thereafter, in 1944, Avery, MacLeod, and McCarty demonstrated that DNA contained a gene's heritable information (by demonstrating that it could transform harmless bacteria into a lethal strain).[8] Hershey and Chase added to the evidence that DNA, not protein, was the heritable material with experiments in 1952[9] by labeling DNA and protein with different radioactive isotopes and following the fate of those isotopes from parent to progeny.

Watson and Crick completed the puzzle by elucidating the structure of DNA as a double helix.[10] The revelation that nucleotide bases on one strand paired with complementary bases on the other immediately suggested a mechanism for the replication of DNA and the mode of inheritance of traits from nucleic acid sequences. Jacob and Monod subsequently defined the gene as a discrete sequence of DNA, transcribed by cellular machinery into messenger RNA and then subsequently translated into protein.[11] The definition

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[8] *See* Oswald T. Avery et al., *Studies on the Chemical Nature of the Substance Inducing Transformation of Pneumococcal Types: Induction of Transformation by a Desoxyribonucleic Acid Fraction Isolated from Pneumococcus Type III*, 79 J. EXPERIMENTAL MED. 137 (Feb. 1944), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2135445/pdf/137.pdf.

[9] *See* Alfred D. Hershey & Martha Chase, *Independent Functions of Viral Protein and Nucleic Acid in Growth of Bacteriophage*, 36 J. GEN. PHYSIOLOGY 39 (Sept. 1952), *available at* http://jgp.rupress.org/content/36/1/39.full.pdf.

[10] *See* James D. Watson & Francis H. Crick, *Molecular Structure of Nucleic Acids: A Structure for Deoxyribose Nucleic Acid*, 171 NATURE 737 (Apr. 1953), *available at* http://www.nature.com/nature/dna50/watsoncrick.pdf.

[11] *See* François Jacob & Jacques Monod, *Genetic Regulatory Mechanisms in the Synthesis of Proteins*, 3 J. MOLECULAR

of "gene" as an encoder for instructions for protein synthesis became dogma in molecular biology for approximately 20 years.

But genome sequencing and other technological innovations have revealed a far more complex and interconnected genomic landscape. Scientists now appreciate that *noncoding* nucleic acid sequences control the expression of many *coding* sequences and perform other cellular functions. Furthermore, these noncoding domains and the sequences they control may combine in networks of interacting elements *that change during development.* Consequently, the environment or the tissue context in which genes operate may lead to alternate sequence elements or to regulatory changes and functional differences. Scientists no longer understand a "gene" purely as the coding sequence of nucleotides that provides instructions for the synthesis of a particular protein. Instead, the continually evolving notion of a gene now includes both coding and noncoding nucleotide sequence features that operate in interconnected and subtle ways to determine the functional attributes and heritable characteristics of an organism.[12]

BIOLOGY 318 (June 1961), *available at* http://www.pasteur.fr/ip/resource/filecenter/document/01s-000046-03t/genetic-regulatory.pdf.

[12] *See* John A. Stamatoyannopoulos, *What does our genome encode?*, 22 GENOME RES. 1602 (Sept. 2012), *available at* http://genome.cshlp.org/content/22/9/1602.full.pdf+html; Jennifer Harrow et al., *GENCODE: The reference human genome annotation for The ENCODE Project*, 22 GENOME RES. 1760 (Sept. 2012), *available at* http://genome.cshlp.org/content/22/9/1760.full.pdf+html.

C. The Basic Features of Genome Sequencing

Genetic sequencing means determining the precise molecular arrangement of nucleotides in some or all of an individual's DNA, one base pair at a time. It is true that there are other, well-established genetic tests that do not involve sequencing. For instance, fluorescent *in situ* hybridization (FISH) can identify structural mutations, but only those that are large enough to be observed through a microscope. Polymerase chain reaction (PCR) techniques can confirm the existence of known mutations associated with a particular disorder. But tests such as these have neither the utility nor the overall promise of sequencing. For example, pathological conditions may arise from mutations that have not been previously well-characterized, and a single experiment or reaction using these techniques targets only a few mutations. Researchers and clinicians must generally have a good idea of what they are looking for before they order these tests. Because different genotypes can cause the same phenotype, moreover, there might well be a genetic basis for the trait or condition that the ordered test simply fails to reveal.

By contrast, knowledge of the actual sequence of nucleotides gives a complete picture of the portion of DNA at issue or, in the case of WGS, of the entire genome. Acquiring this information has been possible for less than 40 years, and has been practical only in the few years since advances in sequencing technology have dramatically accelerated the speed and reduced the cost of DNA sequencing. *See* HHS Report at 49 ("Such multiplex testing can be useful when a condition involves multiple genetic factors or when one wants to simultaneously test for multiple conditions that have one or more potential genetic

causes. In the past, when multiple genetic markers had to be tested, each genetic marker would be tested in a separate test, making testing complex, time-consuming, and expensive.").

1. The Mechanism of Conventional Sequencing

In 1975, Sanger and Coulson described the method of genome analysis that would dominate the industry for the next 30 years.[13] The first step involves breaking open the cell wall to isolate the DNA, then extracting and purifying the DNA from other cellular constituents and biochemicals that bind to the DNA molecule.

Sequencing occurs in several steps. First, the double helix DNA molecule to be sequenced is separated ("denatured") into its two component strands. One of these may be referred to as the "template strand," and the other the "complementary strand." The denatured strands are placed in a "soup" containing all four nucleotides, A, T, C, and G. Most exist in their natural form (dNTPs, where "N" denotes any of the four nucleotides). But there is a comparatively small number that exist as *di*deoxynucleotides (ddNTPs). Both forms will naturally seek a corresponding nucleotide on the template strand, in effect forming a new complementary strand. Because the ddNTPs lack the hydroxyl group to which additional nucleotide bases can attach, however, any new strand formation will end when a ddNTP attaches.

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[13] *See* Frederick Sanger & Alan R. Coulson, *A rapid method for determining sequences in DNA by primed synthesis with DNA polymerase*, 94 J. MOLECULAR BIOLOGY 441 (May 1975), *available at* http://www.sciencedirect.com/science/article/pii/0022283675902132.

To start the sequencing reaction, a short complementary primer molecule is attached to one end of the template strand, and a DNA polymerase enzyme catalyzes the formation of the new strand. The individual nucleotides begin to form hydrogen bonds with the corresponding base on the template strand, extending the new strand, one base at a time, in the 5' to 3' direction. Whenever a ddNTP randomly attaches to the growing strand, however, the absence of a 3' hydroxyl (OH) group precludes further strand extension. The process terminates as to that strand, and the ddNTP marks the last complementary base added in the sequencing reaction. The number of base pairs in the new chain, between the primer and the ddNTP, defines the length of the "read." Because there are many fewer ddNTP molecules than "normal" nucleotides in the mixture, ddNTPs will terminate the newly synthesized strand randomly, resulting in reads of every possible length, up to the longest read length in the process. Significantly, the ddNTPs terminating the new strand are chemically labeled, typically with a dye or fluorophore that facilitates detection of the specific ddNTP terminating each read.

To determine the sequence of the newly synthesized strand, the strands are separated and transferred to a gel or capillary tube in an electric field. The shorter reads move through the field more quickly than do longer reads. As the reads of every length emerge, arranged from shortest to longest, they pass through a laser, which illuminates the dye-labeled ddNTP, identifying the terminating nucleotide. This allows determination of the base sequence of the DNA. Bioinformatic techniques stitch overlapping reads together, revealing the nucleotide

sequences of the relevant portion of DNA or, potentially, of the entire genome.

Stitching isolated reads back into a larger sequence requires many sequencing operations to ensure accuracy and completeness. Thus, the most important technological advances in sequencing are those that have enabled an increasing number of parallel sequencing operations. In the years following publication of Sanger's method, researchers developed capillary electrophoresis devices that dramatically increased throughput.[14] As this technology progressed, Sanger sequencing evolved from requiring a lab bench full of gel slabs processing hundreds of base pairs in each run to a single machine with 96, and eventually 384, capillaries processing tens of thousands of base pairs in parallel. In less than four decades, the amount of information that a sequencing operation can reveal has consistently increased as the price of sequencing has consistently fallen.

Sanger biochemistry ultimately led to the mapping of a complete human genome. In 2001, the Human Genome Project Consortium and Celera Genomics simultaneously published their separate reports, describing the first drafts of the human genome sequence.[15] Having a reference genome for

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[14] *See* Harold Swerdlow et al., *Capillary Gel Electrophoresis for DNA Sequencing: Laser-induced Fluorescence Detection with the Sheath Flow Cuvette*, 516 J. CHROMATOGR. 61 (Sept. 1990); Tim Hunkapiller et al., *Large-scale and Automated DNA Sequence Determination*, 254 SCIENCE 59 (Oct. 1991).

[15] *See* J. Craig Venter et al., *The Sequence of the Human Genome,* 291 SCIENCE 1304 (Feb. 2001); International Human Genome Sequencing Consortium, Eric S. Lander et al., *Initial Sequencing and Analysis of the Human Genome,* 409 NATURE 860 (Feb. 2001).

comparison, coupled with the advances in technology, has made it possible to identify sequence variants by comparison to the reference sequence. Alignment and mapping of sequence reads to the reference genome has also enabled complete genome sequences of individuals (i.e., other than the reference genome). Significantly, mapping to a reference bypasses the more complex, expensive, and time-consuming task of *de novo* genome assembly. The human genome project also spurred the development of many "next-generation sequencing" methods, further accelerating the breathtaking pace of scientific discovery.[16]

2. The Promise of Next-Generation Sequencing

Genformatic emphasizes two points with respect to the evolution of gene sequencing. First, although sequencing has been possible for less than 40 years, the advances have been remarkable. With continuing advances in next-generation techniques, the possibilities are almost endless. To put the advances into context, Sanger sequencing can process only up to 384 samples in parallel, even with the advances in technology. Next-generation sequencing includes cyclic-array strategies in which "hundreds of millions of sequencing reads can potentially be obtained in parallel." Shendure 2008 at 1136. As capabilities have expanded, sequencing increasingly has become

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[16] A detailed analysis of "next generation" sequencing is far beyond the scope of this brief and is unnecessary for the resolution of the issue presented in this case. For a general overview, see Jay Shendure & Hanlee Ji, *Next-generation DNA sequencing*, 26 NATURE BIOTECHNOLOGY 1135 (Oct. 2008) ("Shendure 2008"), and Jay Shendure & Erez Lieberman Aiden, *The expanding scope of DNA sequencing*, 30 NATURE BIOTECHNOLOGY 1084 (Nov. 2012) ("Shendure 2012").

a basic tool of life science. "Sequencing is emerging as a ubiquitous, digital 'readout' for the deep, comprehensive exploration of genetics, molecular biology and cellular biophysics." Shendure 2012 at 1092. Indeed, those in the industry expect it to dominate the entire life science field for the near future and to provide important new tools for clinical medicine.

> Today, sequencing has an increasingly fundamental role in the genetic analysis of human disease and model organism phenotypes as well as in addressing basic questions in organismic and cellular biology. . . . We predict that much of the agenda of biology in the coming decade will be driven in large part by the scientific opportunities afforded by next-generation DNA sequencing technologies.

Id. at 1084.

As technology has advanced, accessibility has increased. Newer sequencing instruments "have fewer infrastructure requirements." Shendure 2008 at 1141. Concomitantly, "[t]he cost of DNA sequencing has plummeted since 2005, from $1,000 per megabase down to a mere ten cents per megabase." Shendure 2012 at 1084 (citation omitted). "The reduction in the costs of DNA sequencing by several orders of magnitude is democratizing the extent to which individual investigators can pursue projects at a scale previously accessible only to major genome centers." Shendure 2008 at 1143.

With the advances in technology, the decrease in cost, and the increase in accessibility, sequencing is poised to move from purely research applications to commercial applications as well. It will soon be possible to sequence an individual's whole genome

for less than $1,000.[17] The practice of medicine to date has relied on treatment regimens (including pharmaceutical formulations) generalized to the entire population. This necessarily leads to much trial and error in selecting an effective treatment regimen, as well as to many adverse effects in patients for whom a particular treatment regimen might be harmful. Armed with an individual's entire genetic code, health care providers and pharmaceutical companies will be able to tailor treatment and target conditions to an extent that has been unimaginable to date.[18] Sequencing provides the major stimulus in the evolution to personalized medicine.[19]

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[17] *See* Kevin Davies, *The $1,000 Genome: The Revolution in DNA Sequencing and the New Era of Personalized Medicine* (Free Press, New York 2010).

[18] As with all technological advances, society will have choices to make with respect to such issues as accessibility of genetic information and privacy concerns. *See*, *e.g.*, Bonnie Rochman, *The DNA Dilemma: A Test That Could Change Your Life*, TIME, Dec. 24, 2012, at 42. Genformatic does not belittle these concerns and proactively considers them in its business plan. But these concerns do not eliminate the benefits that sequencing can provide to individuals and to our society as a whole.

[19] The advances in technology have allowed sequencing to progress from individuals to entire populations. Genome-wide association studies ("GWAS") have generated a rapidly increasing body of knowledge about genetic markers associated with a phenotype of interest (e.g., stroke, multiple sclerosis, or breast cancer). GWAS studies are conducted by identifying thousands of individuals with a phenotype of interest and genotyping those "cases" for hundreds of thousands of genetic markers(typically single nucleotide polymorphisms, or "SNPs"), then comparing the incidence of particular genotypes in cases to the incidence of genotypes in a similar "control" group (which lack the phenotype of interest). Statistical analysis of GWAS data allows

Second, although there are differences among the various next-generation methods, "the great variety of sequencing experiments is a result of distinct combinations of a relatively small set of core techniques." Shendure 2012 at 1091, fig. 3. The advances in next-generation sequencing primarily involve the actual sequencing operations. As with Sanger sequencing, however, the first step remains isolating, purifying, and fragmenting the DNA molecule. Thus, next-generation sequencing remains equally vulnerable to patents on naturally occurring nucleotide sequences.

To put the numbers into context, the Sanger method can sequence a read of up to approximately 1,000 base pairs. The read lengths in next-generation sequencing vary from less than 20 base pairs to several hundred. *See* Shendure 2008 at 1140, table 1; Shendure 2012 at 1187, table 2. Only one sequencing instrument currently available can sequence reads longer than 1,000 base pairs.[20] *See*

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identification of markers associated with the phenotype of interest. For a brief overview and a searchable database, see http://www.genome.gov/gwastudies/.

Note that GWAS studies do not necessarily identify causal mutations, but rather sequence variants linked to a trait. This association allows assignment of an individual to a higher or lower relative-risk category for a particular phenotype depending on the presence or absence of a SNP in their genome. The explosion of GWAS is illustrated by a time series depiction of the rapidly expanding catalogue of GWAS markers and traits. *See* http://www.ebi.ac.uk/fgpt/gwas/#timeseriestab. As GWAS studies move from genotyping hundreds of thousands of SNPs to WGS, the rate of knowledge generation will only accelerate, increasing the probability of identifying causal mutations for disease and other traits.

[20] A higher error rate in calling individual bases tempers this read length advantage. *See* http://www.pacificbiosciences.com/pdf/Poster_High_Throughput_Long_Read_PacBio_RS.pdf.

Shendure 2008 at 1140, table 1; Shendure 2012 at 1187, table 2. Comparing current read lengths to the 3 billion base pairs in the entire human genome, distributed among 23 pairs of chromosomes, it is clear that even the most advanced sequencing technology currently available must isolate, purify, and fragment relatively tiny sequences of nucleotides as a necessary first step. As technology continues to advance, read lengths should continue to increase and costs should continue to decrease. Eventually, there will be a sequencing method that will produce fast, accurate sequence reads comprising tens of thousands of base pairs or more.

II. ALLOWING PATENTS ON NATURALLY OCCURRING NUCLEOTIDE SEQUENCES THREATENS TO INHIBIT FUTURE INNOVATION

Enforcement of patents on naturally occurring nucleotide sequences threatens to inhibit these advances.

A. The Implications of Patent Rights in Naturally Occurring Nucleotide Sequences

The ’282 patent contains the following claims:

> 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.
>
> 6. An isolated DNA having at least 15 nucleotides of the DNA of claim 2.

JA822. As their wording suggests, both of these are dependent claims, referencing claims 1 and 2 of the ’282 patent.[21] Although claim 1 and claim 2

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[21] The ’282 patent covers BRCA1. Claim 5 of the ’492 patent, covering BRCA2, is analogous to claim 5 of the ’282 patent.

ultimately claim the same thing – the nucleotide sequence of the BRCA1 gene – they do so from two different angles. Claim 1 refers to the polypeptide synthesized by the BRCA1 gene, defining the nucleotide sequence by what it makes. Claim 2 refers to the sequence of the DNA itself.

The BRCA1 sequence in Myriad's claim 2 (which includes both coding and noncoding portions) is 5,914 base pairs in length, JA822 (claim 2). Because they refer back to claims 1 and 2, claims 5 and 6 cover any sequence "having at least 15 nucleotides" ("15mers"), occurring anywhere along a length of almost 6,000 nucleotides.

Consider that (i) the entire human genome consists of approximately 3 billion nucleotide base pairs, (ii) there are only four nucleotides in DNA, A, T, G, and C, and (iii) modern sequencing methods must first isolate, purify, and segment DNA into reads that typically range from 30 to 1,000 base pairs in length. Given these facts, it is mathematically inevitable that sequences "having at least 15 nucleotides of the DNA of claim 1" will occur somewhere in a genome consisting of a 3 billion base pair sequence of nucleotides. Consequently, it seems inevitable that nucleotide sequences within the express language of these claims will be isolated in the course of sequencing any human genome.

The actual calculations confirm this inevitability. A team of researchers worried that "[o]ne of these claims seemed to us particularly broad, so we investigated it, doing simple calculations to estimate its

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5. An isolated DNA molecule comprising at least 15 contiguous nucleotides of the DNA molecule of claim 1.

JA1028.

reach." Kepler, 95 GENOMICS at 312. They observed that claim 1 of the '282 patent embodies approximately 1.6 million 15mer sequences, estimating that there are approximately 15 infringing sequences *per human gene* of average length. *Id.* at 313. To experimentally confirm this estimation, the researchers focused on chromosome 1. They empirically verified "over 340,000 matches of claimed 15-mers to the 250 million base pairs of chromosome 1," indicating "about 14 infringing sequences per human gene." *Id.* Not surprisingly, the researchers concluded that "[t]his claim and others like it turn out, on examination, to be surprisingly broad, and if enforced would have substantial implications for medical practice and scientific research." *Id.* at 312.

B. The "Bright Line Prohibition" Against Patenting Natural Phenomena

Even those who support gene patentability under § 101 do not disagree. On October 28, 2010, Professors Christopher M. Holman and Robert Cook-Deegan submitted an *amicus* brief in this case in the court of appeals. This was in the first appeal to the Federal Circuit, prior to this Court's opinion in *Mayo*. With respect to claim 5 of the '282 patent, they wrote that, "[i]n principle, fragment claims such as this provide much broader coverage than claims reciting full-length genes, and would appear to encompass conventional BRCA mutation testing that involves the amplification and analysis of DNA fragments as used in diagnostic testing."[22] The professors demonstrated the breadth of this claim:

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[22] Brief of Amici Curiae Christopher M. Holman and Robert Cook-Deegan in Support of Neither Party at 20, *Association for Molecular Pathology v. United States Patent & Trademark Office*,

> In particular, a recent study found that 80% of the cDNA and mRNA sequences that were contributed to GenBank (and hence presumably published) before the effective filing date of the '282 patent contain at least one DNA fragment falling within the scope of Claim 5, and thus would apparently be encompassed by the claim. [Kepler]. Follow-up studies have shown many "hits" of 15-mer sequences in GenBank sequences that had already been deposited more than a year before patent application, thus implicating 35 USC 102(b).

Holman Amicus Br. at 20-21.

By opining that the sheer breadth of claim 5 would ultimately cause it to fail for lack of novelty, they supported their broader point: that courts should address patents on human genes "more surgically and appropriately . . . with other patent law doctrines [such as claim construction, anticipation, non-obviousness, and written description], or legal and policy solutions addressing problematic enforcement practices" rather than under § 101. *Id.* at 4-5, 20-21. But this ignores a critical issue. Myriad drafted claims 5 and 6, and the USPTO granted the '282 patent, including those claims. Those claims are currently part of an existing United States patent, entitled to the presumption of validity in 35 U.S.C. § 282. And, while "Myriad has only rarely enforced its patents in research, [it] has vigorously enforced its patents against commercial genetic testing, and has selectively enforced its patents in clinical research. . . . *BRCA* research in the United States continues

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653 F.3d 1329 (Fed. Cir. 2011) (No. 2010-1406) (filed Oct. 28, 2010) ("Holman Amicus Br."), 2010 WL 4853323.

only with Myriad's indulgence." Kepler, 95 GENOMICS at 313.[23]

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[23] Myriad's past conduct undermines trusting its continued indulgence.

> The fact that Myriad has allowed research to go forward – most of which infringes its intellectual property – is laudable, but tempered by distrust. If Myriad had a reason to go after researchers, would it do so? *Indeed, it has*.
>
> Myriad restricted *BRCA* testing for clinical research by suing OncorMed and the University of Pennsylvania. All testing at the time was part of research, including trials funded by the National Cancer Institute. Myriad's definition of permissible "research" testing by others was quite narrow; its definition of appropriate testing in its own laboratory, however, was expansive, including clinical testing performed at a time when all health professional recommendations urged testing only in the context of research. OncorMed agreed to test only in research protocols, and Penn was a testing core for multi-institutional trials. It was Myriad that broke from professional standards to do clinical testing outside of research protocols in the early years. *Myriad thus exercised its patent exclusivity in two ways: to establish a U.S. service monopoly and flout clinical guidelines in its own testing and to impose a narrow definition of research on others' BRCA testing*. The Supreme Court may decide "Progress in Science and the useful Arts" is better served by clear legal limits on what can be patented at all, rather than leaving decisions about freedom to do research with patent-holders.

Robert Cook-Deegan, *Law and Science Collide Over Human Gene Patents*, 338 SCIENCE 745, 747 (Nov. 2012) (footnotes omitted, emphases added), *available at* http://people.duke.edu/~ab389/PubList/BCD%20SCience745.full.pdf.

Myriad's gene patents have also empowered it to construct and maintain a proprietary library of gene testing results. *See* Robert Cook-Deegan et al., *The Next Controversy in Genetic Testing: Clinical Data as Trade Secrets* 2 (Nov. 14, 2012) (advance

More importantly, the Court squarely rejected this argument in *Mayo*. "This approach . . . would make the 'law of nature' exception to § 101 patentability a dead letter. The approach is therefore not consistent with prior law." 132 S. Ct. at 1303. The argument that claims 5 and 6 of the '282 patent are so broad that they cannot be valid presents the flipside of the patent holder's argument in *Mayo*. There, the holder "argue[d] that, because the particular laws of nature that its patent claims embody are narrow and specific, the patents should be upheld." *Id.* But the Court refused to resolve the § 101 inquiry based on the breadth or narrowness of the claims, observing that:

> Courts and judges are not institutionally well suited to making the kinds of judgments needed to distinguish among different laws of nature. And so the cases have endorsed a bright-line prohibition against patenting laws of nature, mathematical formulas and the like, which serves as a somewhat more easily administered proxy for the underlying "building-block" concern.

Id. Claims 5 and 6 illustrate the wisdom of this approach. Because a nucleotide sequence is a natural

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online publication; to be published at — EUR. J. HUM. GENETICS —) ("Myriad has access to public databases in interpreting mutations, but outsiders do not have access to Myriad's database."), *available at* http://www.nature.com/ejhg/journal/vaop/ncurrent/pdf/ejhg2012217a.pdf. Hoarding data in this manner has significant implications for WGS. "In an environment in which new technologies, including whole-genome and whole-exome sequencing, are already beginning to change clinical practices in genetic testing, a proprietary database gives Myriad indefinite exclusivity independent of patent protection." *Id.*

phenomenon, it is not patent-eligible under § 101 – no matter its length.

C. Not "Debunking the Myth," But Proving the Point

If the Court allows patents of naturally occurring nucleotide sequences under § 101, genome sequencers face significant practical difficulties. Professor Holman, in attempting to "debunk the myth" that WGS infringes patents such as the patents in suit, underscored these difficulties. To address the "misconception" that "20% of human genes are patented," he contacted the author of the article cited for that proposition, *see* Kyle Jensen & Fiona Murray, *Intellectual Property Landscape of the Human Genome*, 310 SCIENCE 239 (2005), and obtained a list of the 4,270 "gene patents" cited in the article. Holman, 30 NATURE BIOTECHNOLOGY at 240-41. His review of these patents reveals the enormity of the task: "Each patent contains multiple patent claims, sometimes hundreds of claims, so to make my task *manageable* I randomly selected 533 of the 4,270 patents and reviewed all of the claims in each of these patents." *Id.* at 241 (emphasis added). In other words, the "unmanageability" of the task led him actually to review only 12.5% of the cited patents.

Nonetheless, his results were telling. He found that 369/533 patents he examined – 69.2% – claimed "DNA molecules that correspond in sequence to at least some portion of a human gene," presumably because these claims "explicitly mentioned" "at least some portion of the gene's DNA sequence, or the amino acid sequence of the corresponding protein." *Id*. Assuming that his sample was representative, and multiplying the entire sample by the percentage

he found, his findings indicate that there are 2,856 U.S. patents that claim patent rights to a portion of a naturally occurring nucleotide sequence in a human DNA molecule.

Despite these overwhelming numbers, Professor Holman concluded that a construction of such claims that is broad enough to endanger gene sequencing would likely lead a court to declare the patent invalid. Specifically, he focuses on the widespread use of the word "isolated" in drafting claims, *id.*, claim language that Myriad has used in the claims at issue. Professor Holman acknowledges that Professor Cook-Deegan "believes that any technology for reading a DNA sequence will necessarily involve isolation and thus constitute infringement if the term 'isolated' is interpreted broadly, a possibility he feels cannot be ruled out," and agrees that "it is impossible to entirely rule out the possibility that a court would interpret a claim to an isolated DNA molecule in the extremely broad sense suggested by Cook-Deegan." *Id.* at 242.[24] Yet Professor Holman is Myriad's primary authority for the proposition that WGS does *not* infringe its patents. *See* Opp. 6, 16.

Professor Holman does acknowledge the uncertainty inherent in relying on claim construction to police overreaching patents. He observes that "the interpretation of patent claims, particularly outside the context of patent infringement litigation, is a notoriously unpredictable undertaking" that is

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[24] This "possibility" would be consistent with the Manual of Patent Examining Procedure (rev. ed. Aug. 2012), which stipulates that claims be given their "broadest reasonable interpretation." MPEP § 2111. The court of appeals has endorsed broad interpretation in the context of claim construction. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1316 (Fed. Cir. 2005) (en banc).

"especially pronounced with respect to gene patents." Holman, 30 NATURE BIOTECHNOLOGY at 241. Because "[i]t is not uncommon for the Federal Circuit judges to disagree among themselves as to the proper interpretation of a claim," "some, including at times the Federal Trade Commission, [have] characterize[d] patents as mere 'probabilistic' property rights." *Id.* Nonetheless, he concludes that "the vast majority of these patents would almost certainly not be infringed by WGS, either because they are not gene patents at all, or because they only claim isolated DNA molecules unlikely to be produced in WGS." *Id.* at 244. In any event, he opines that any award of damages for infringement "would most likely be minuscule considering the relative contribution of the patented invention to the sequencing of the entire genome." *Id.*

Far from "[d]ebunking the myth that [WGS] infringes thousands of gene patents," Professor Holman's analysis confirms that there are almost 3,000 U.S. patents whose claims "explicitly mention[]" "at least some portion of the gene's DNA sequence, or the amino acid sequence of the corresponding protein." *Id.* at 240, 241. His reliance on the ultimate invalidity of claims to police overreaching largely leaves the patenting of naturally occurring nucleotide sequences to the "notoriously unpredictable undertaking" of claim construction. *Id.* at 241.

Genformatic asserts that his approach improperly tasks courts and judges with determining the degree to which exclusive rights to naturally occurring sequences of nucleotides inhibit future innovation, a task to which they "are not institutionally well suited." *Mayo*, 132 S. Ct. at 1303. The better approach is to confirm the "bright-line prohibition" against

patenting natural phenomena, thereby avoiding the "danger that becomes acute when a patented [composition] . . . forecloses more future invention than the underlying discovery could reasonably justify." *Id*. at 1301, 1303.

D. The Inhibition of Innovation

A decade ago, a group of professors and researchers interviewed 122 directors of U.S. laboratories performing DNA-based genetic tests. They found that "[t]wenty-five percent of respondents reported that they had stopped performing a clinical genetic test because of a patent or license. Fifty-three percent of respondents reported deciding not to develop a new clinical genetic test because of a patent or license. In total, respondents were prevented from performing 12 genetic tests, and all of these tests were among those performed by a large number of laboratories."[25] The cause was not difficult to ascertain: "Almost two-thirds of the laboratory directors in our sample had been contacted by a patent- or license-holder about the laboratory's potential infringement of a patent by performance of a genetic test." Cho, 5 J. Molecular Diagnostics at 5-6 (discussion).

> We conclude that patents and licenses have a significant negative effect on the ability of clinical laboratories to continue to perform already developed genetic tests, and that these effects have not changed substantially throughout the past 3 years. Furthermore, the development of new genetic tests for clinical use, based on

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[25] Mildred K. Cho et al., *Effect of Patents and Licenses on the Provision of Clinical Genetic Testing Services,* 5 J. Molecular Diagnostics 3, 3 (Feb. 2003), *available at* http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1907368/pdf/0108.pdf.

> published data on disease-gene associations, and information sharing between laboratories, seemed to be inhibited.

Id. at 8 (conclusion). Notably, BRCA1/BRCA2 were among the genes whose patent holders had contacted the labs. *Id.* at 5 (Effects of Patents and Licenses on Clinical Genetic Testing Services).

In 2010, the Secretary's Advisory Committee on Genetics, Health, and Society confirmed "that patents have been used to narrow or clear the market of existing tests, thereby limiting, rather than promoting availability of testing." HHS Report (transmittal letter). The advisory committee emphasized the danger to innovation: "The substantial number of existing patents on genes and methods of diagnosis also pose a threat to the development of multiplex testing, parallel sequencing, and whole-genome sequencing, the areas of genetic testing with the greatest potential future benefits." *Id.*

To avoid infringement proactively, sequencers of multiple genes or of the whole genome must identify, then try to license, all genes involved in the proposed test. "The alternative of leaving patented genes out of a multiplex test or not reporting the results pertaining to those genes undermines the very clinical utility of multiplex analysis." *Id.* at 50. But identifying, contacting, and reaching an agreement with the patent holders presents enormous difficulties. The advisory committee discovered that ownership of the 4,270 "gene patents" identified in Jensen & Murray's 2005 article was distributed among 1,156 different assignees.

> The existence of so many patents protecting genes, spread among various assignees, creates

> a "patent thicket" – "a dense web of overlapping intellectual property rights that a company must hack its way through in order to actually commercialize new technology." To hack through this thicket to develop a multiplex test, a developer would face several challenges. The developer first would have to identify all the patents requiring licenses. This effort would involve a costly search for relevant patents and an analysis of their claims to determine whether the proposed multiplex test would infringe each particular claim. Once the patents relevant to the test were identified, the developer would have to determine whether licenses were available for each patent. The case studies revealed that such licensing information often is difficult to obtain. Finally, the developer would have to separately negotiate licenses with each individual patent holder.

Id. at 51 (footnote omitted). Although Professors Holman and Cook-Deegan argue that more "surgical[]" doctrines such as claim construction would eventually cure the problem,[26] Holman Amicus Br. at 5, they have acknowledged that, "[i]f 'isolated' is so expansive that full-genome sequencing infringes thousands of individual gene claims, then a serious patent thicket could arise," *id.* at 19-20.

Sequencers could avoid the problem, at least temporarily, by proceeding with development, then

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[26] To be clear, Genformatic hopes that Professors Holman and Cook-Deegan are correct and indeed believes that there is a likelihood that *all* patents on naturally occurring nucleotide sequences in DNA would eventually be invalidated. But allowing such patents to bypass § 101 effectively sanctions the inhibition of innovation in contravention of this Court's directives.

defending any infringement suits as they appear. The advisory committee advised against this approach, however, noting that innovators who have already funded projects are "easier prey for patent holders." HHS Report at 52. "Choosing to proceed with a product involves the risk of being sued, and the expense of defending against suits that arise diverts funds that could otherwise be used for innovation." *Id*. Avoidance of potential problems is frequently the best alternative: "the numerous existing patent claims on genes are already affecting the use, if not the development, of multiplex tests in that clinicians are not reporting the results for patent-protected genes in multiplex tests for fear of inviting a lawsuit." *Id.* at 54. Of course, not reporting the entire sequence revealed by WGS defeats the purpose and dulls the promise of combining all available genetic tests into one. Moreover, WGS potentially detects almost all sequence variations, enabling subsequent reanalysis of WGS results to survey for newly identified pathological genetic variation as those discoveries are made.

Turning to a direct discussion of WGS, the advisory committee acknowledged that, because of "the distinct possibility that some patent claims on genes will be infringed by whole-genome sequencing, these patents remain a concern as a potential barrier to the development of whole-genome sequencing." *Id.* at 58. The committee concluded:

> In sum, it appears that test manufacturers are eager to develop – and clinicians are eager to use – multiplex tests, rather than single-gene tests, to carry out genetic testing. These tests would be more efficient than conducting a series of individual tests. Patent claims on isolated

> genes and association patent claims, however, appear to have already created a thicket of intellectual property rights that may prevent innovators from creating these multiplex tests. Similar concerns arise when envisioning the clinical application of whole-genome sequencing. Such scenarios threaten to diminish the usefulness of these promising technologies and their application to patient care.

Id. at 61. Genformatic asserts that this is exactly the sort of inhibition of "future innovation" that concerned the Court in *Mayo*. 132 S. Ct. at 1301, 1303.

CONCLUSION

The judgment of the court of appeals should be reversed, and the patents held invalid.

Respectfully submitted,

DANIEL BINFORD WEAVER
6301 Highland Hills Drive
Austin, Texas 78731
(512) 565-4693

EARL LANDERS VICKERY
Counsel of Record
LAW OFFICE OF LANNY VICKERY
3007 Dancy Street
Austin, Texas 78722
(512) 435-6666
(lanny@justiceseekers.com)

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